

Structural Features of Prolactins and Growth Hormones That Can Be Related to Their Biological Properties*

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IN THIS review we have compared the amino acid sequences of the GHs of eight mammalian species and the domestic chicken with the sequences of the PRLs of seven mammalian species. Individual amino acids, clusters of residues, and regions of the molecules were identified that were highly conserved among all of the hormones. Other individual amino acids, clusters of residues, and regions were identified that were specific to PRLs only or to GHs only. Attempts were made to associate these hormone-specific and commonly conserved features to the hormone-specific and shared biological properties of PRLs, GHs, and placental lactogens (PLs) by relating them to predicted secondary structure and hydropathy analysis. The latter involves predicting which regions of the molecules would be interior or exterior, based on the hydrophobicity or hydrophilicity of the regions.

External clusters of conserved residues (consisting of both hormone-specific and commonly conserved) were identified that could be specifically associated with molecules that have GH activity or with those with lactogenic activity [including human (h) GH and PL]. Other external clusters were conserved in common among the PRLs and the GHs. The validity of our proposal that certain clusters of residues may be associated with GH and PRL binding determinants found support from the known structure and properties of two variant forms of hGH (i.e. 20 K and hGH-V). The residues that are likely to be responsible for hGH having PRL activity and for hPL not having GH activity were also identified.

These analyses, in conjunction with comparative data on the biological properties and receptor binding activities of PRLs, GHs, and PLs, led us to propose that hormone and species specificities in the actions of these hormones are determined more by hindrance determi-

nants on the hormones and their receptors, than by differences in binding domains.

Introduction

PRLs, GHs, and placental lactogens (PLs) are generally considered to belong to an hormonal family because they share a number of common biological, immunological, and structural features (1-5). Although recent evidence indicates that a small proportion of some PRLs may be glycosylated (6), most of the members of the PRL-GH family are simple proteins of about 190-200 amino acids in length. Physicochemical studies indicate that they are all globular proteins with similar conformation and about equivalent α -helical content (3, 4). When the amino acid sequences of the known PRLs and GHs, including salmon(s) PRL (7) and GH (8, 9), and chicken GH (10) are displayed in two dimensions, they all have a small loop of amino acids at the carboxyl terminus, and a larger loop comprising about 70% of their amino acid residues forms a second significant feature of these molecules. Mammalian PRLs are distinctive from GHs in having a second small loop at the amino terminus.

The existing members of the PRL-GH family are thought to be derived from a common ancestral gene which diverged about 4×10^8 yr ago to give rise to the separate PRL and GH lineages (11). Human (h)PL appears to have arisen from one of the hGH genes about 2×10^7 yr ago (11), but the emerging evidence indicates that rat (r) and bovine (b)PL are derived from PRL genes rather than from GH genes (12-15). Thus, primate PLs belong to the GH lineage while rodent and ungulate PLs are members of the PRL lineage. Because of this evidence, we shall group the various members of the GH-PRL-PL family into two subfamilies: those that are PRL related and those that are GH related.

The genes of several mammalian members of these two hormonal subfamilies have been well characterized (11). All of them consist of five exons of relatively

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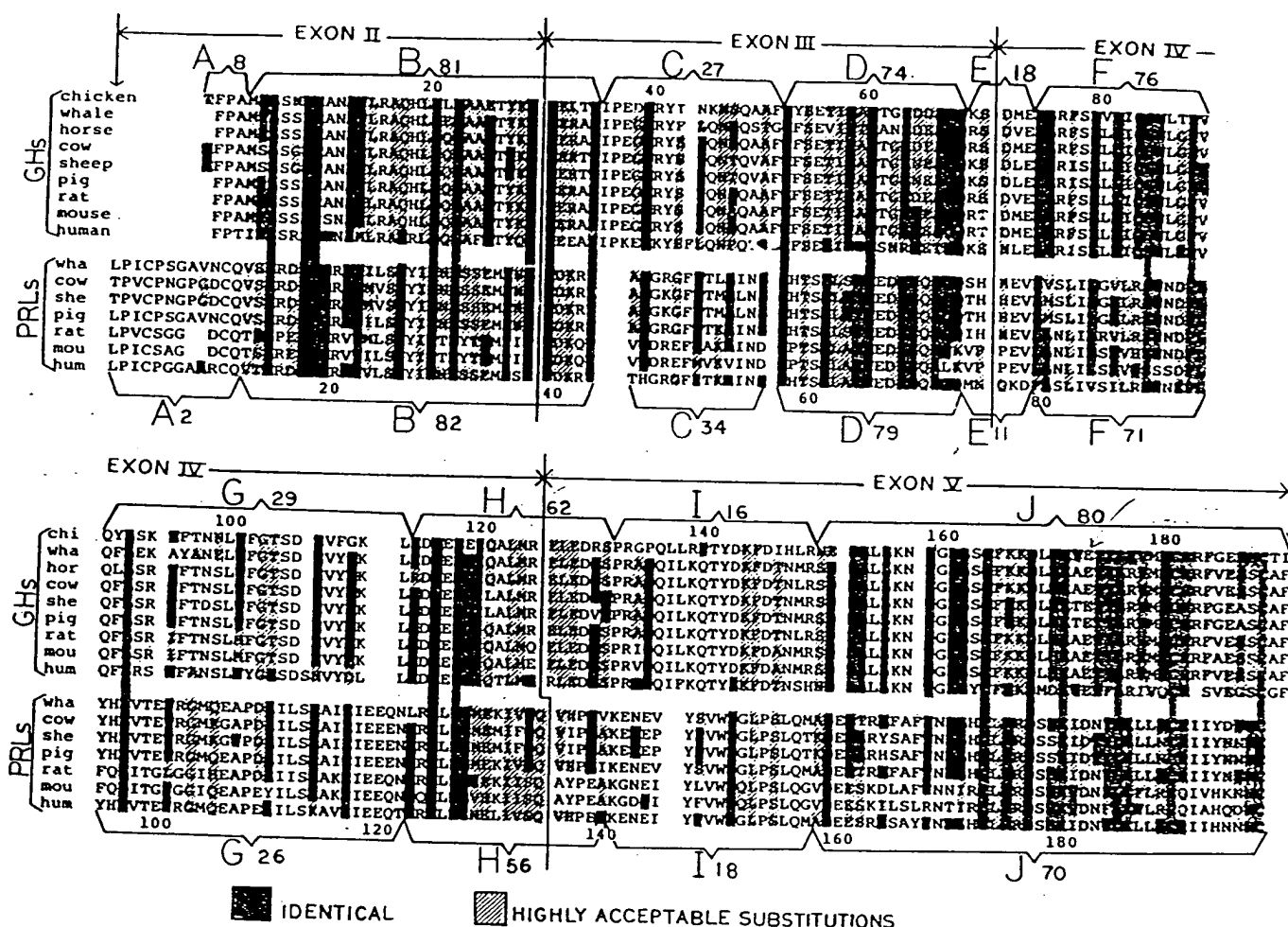


FIG. 1. The complete amino acid sequences of the GHs and the PRLs of various homeothermic species aligned to maximize homologies according to Dayhoff (61). The hormones have been divided into 4 segments which represent the individual exons (II-V) that encode the mature protein sequences (11). Residues that are identical among the PRLs and GHs are shaded in dark gray. Those which are invariant among all of the PRLs and GHs are connected by the dark gray stripe extending from the GHs to the PRLs, and those that are highly acceptable substitutions (61) are shaded in light gray. Regions with a high degree of common homology are defined as those in which residues that are homologous among the PRLs and GHs are clustered (i.e. B, D, F, H, and J). Regions A, C, E, G, and I show a low degree of common homology. The numbers above the brackets of the GH sequences and below the brackets under the PRL sequences represent the respective percent total homology for each region. In order to determine this percent homology, invariant residues were given a value of 200, highly conserved residues were given 100, and highly acceptable substitutions were given 50. The sum of these assigned values in a region was divided by the number of residues in it to give the percent homology. The numbers immediately above the GH sequences and immediately below the PRL sequences are residue numbers according to the sequence of hGH and hPRL, respectively. For each number, the first digit is aligned with the numbered residue. The sequences from the chicken (10), pig (62), and mouse (63) GHs and the mouse PRL (63, 64) are from the indicated sources. The sequences of whale GH and PRL which we used are composites of those reported (65-67) for the fin whale and sei whale (*Balaenoptera phusalus* and *B. borealis*, respectively). See Wallis (23) or Miller and Eberhardt (11) for references to other sequences.

hormonal families. Moderately long regions of high homology are also present in exons III (region D) and IV (region F). The latter exon also has a segment of moderate homology that extends into exon V (region H). The longest region of high homology common to both hormonal subfamilies spans most of the exon V segment and extends to the carboxyl termini (region J). The

degree of homology of this segment among the GHs (80%) is higher than that among the PRLs (70%).

Within three of the highly conserved regions the invariant and the identical residues are clustered into groups that delineate segments of even higher conservation. With reference to the numbering sequence of the PRLs, these short segments extend from residues 15-23,